REMARKS/ARGUMENTS

The foregoing amendments in the specification and claims are fully supported by the specification and claims as originally filed, and do not constitute new matter.

Prior to the present amendment, Claims 58-77 were pending in this application and were rejected on various grounds. With this amendment, Claims 58-62 have been amended to further clarify what Applicants have always regarded as their invention. Support for the amendments to the claims is found in the specification at, for example, page 354, line 8, to page 355, line 1.

Claims 58-65, 68-70 and 74-77 are pending after entry of the instant amendment. Applicants expressly reserve the right to pursue any canceled matter in subsequent continuation, divisional or continuation-in-part applications.

Applicants note and appreciate the withdrawal of the earlier objections and rejections under 35 U.S.C. §112, first paragraph, and 35 U.S.C. §112, second paragraph.

The remaining rejections of Claims 58-65 and 68-70 under 35 U.S.C. §102(e) are addressed below.

I. Information Disclosure Statement

Applicants thank the Examiner for considering the Information Disclosure Statement filed on January 26, 2005.

II. Priority Determination

Applicants thank the Examiner for granting the priority of the instant application as February 18, 2000.

III. Claim Rejections Under 35 USC § 102(e) over Parham *et al.*

Claims 58-61 and 74-77 remain rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Parham *et al.*, U.S. Patent No. 6,586,228, filed March 8, 1999. The Examiner states that the rejection is only being made over claims which are directed to nucleic acid molecules that have 80-95% sequence identity to SEQ ID NO:351, wherein the encoded polypeptide has fetal hemoglobin inducing activity. The Examiner asserts that "[t]he nucleic acid

molecule of Parham *et al.* has 98.1% identity with the sequence of SEQ ID NO:351, therefore, the structural limitations of the claims are met." (Page 4 of the instant Office Action).

Applicants respectfully disagree and traverse the rejection. Applicants respectfully submit that Claims 58-61 and 74-77 are not anticipated under 35 U.S.C. §102(e) by Parham *et al.* for the reasons previously set forth in the Applicants' response filed on January 26, 2005, and below.

Applicants respectfully submit that SEQ ID NO: 351 of the instant application comprises 2056 nucleotides. Parham *et al.* discloses a polynucleotide (SEQ ID NO:1) comprising only 1381 nucleotides. The sequence of Parham *et al.* has 1362 matches to SEQ ID NO:351 of the instant application, as shown in the attached sequence alignment (see Exhibit C). This corresponds to only 67.7% sequence identity to the entire length of SEQ ID NO:351. Therefore, Parham *et al.* does not disclose a polynucleotide having at least 80% nucleic acid sequence identity to SEQ ID NO:351, and does not anticipate Claims 58-61 and 74-77 of the instant application.

Accordingly, Applicants respectfully submit that Parham *et al.* is not prior art under 102(e) and the present rejection should be withdrawn.

IV. Claim Rejections Under 35 USC § 102(e) over Thompson *et al.*

Claims 58-65, 69-70, and 74-77 are newly rejected as allegedly anticipated under 35 U.S.C. §102(e) by Thompson *et al.*, U.S. Patent No. 6,610,286, with a priority date of December 23, 1999. The Examiner asserts,

> The nucleic acid molecule of Thompson et al has 99.4% identity with the sequence of SEQ ID NO:351, therefore the structural limiations of the claims are met. Thompson et al. is silent to the biological activity of inducing fetal hemoglobin for the encoded protein, however, because the encoded protein is identical in structure, the biological activity of the encode protein would be inherent, absent evidence to the contrary. (Page 5 of the instant Office Action).

Applicants first respectfully note that the claims, as amended herein, recite nucleic acids wherein the encoded polypeptide inhibits T-cell proliferation in the MLR assay.

Applicants have claimed priority to U.S. Provisional Application Serial No. 60/087,106,

filed on May 28, 1998. The present application is entitled to the priority date of May 28, 1998, which precedes by over 18 months the effective priority date of Thompson *et al.* (December 23, 1999). Applicants further submit that prior to December 23, 1999, it had been determined that PRO1114 inhibits T-cell proliferation in the mixed leukocyte reaction (MLR) assay and has utility in therapeutical applications when inhibition of the immune response is desired, such as in autoimmune diseases or in graft rejection.the effect of this polypeptide on the inhibition of T-cell proliferation. Accordingly, Thompson *et al.* is not prior art against the present application and Claims 63-65 and 68-70 are patentable.

In support, Applicants respectfully submit a Declaration under 37 C.F.R. §1.131 by Dr. Baker, Dr. Goddard, Dr. Godowski, Dr. Gurney, Dr. Tumas and Dr. Wood ("Declaration") that establishes that Applicants had cloned and sequenced PRO1114 and identified its homology to cytokine receptor family proteins, and had determined that PRO1114 was an inhibitor of T-cell proliferation in the MLR assay, before the prior art date of December 23, 1999. The consideration of the Declaration is respectfully requested.

Applicants respectfully submit that an executed copy of the Declaration will be submitted to the Examiner shortly.

As stated in the Declaration, U.S. Provisional Patent Application Serial No. 60/087,106, filed on May 28, 1998, discloses sequences designated as SEQ ID NO:1 and SEQ ID NO:3, which are identical to SEQ ID NO:351 and SEQ ID NO:352, respectively, of the present application. U.S. Provisional Application Serial No. 60/087,106 also discloses that SEQ ID NO:3 has homology to cytokine receptor family proteins.

In addition, a copy of a page from an internal database (with the dates redacted) showing the data from the mixed leukocyte reaction (MLR) assay for the PRO1114 polypeptide sequence is attached to the Declaration as Exhibit B. The assay data shown in Exhibit B indicates that the PRO1114 polypeptide inhibits T-cell proliferation in the MLR assay and has utility in therapeutical applications when inhibition of the immune response is desired, such as in autoimmune diseases or in graft rejection. As evidenced from the report and stated in the Declaration, the MLR assay data shown in Exhibit B was obtained prior to December 23, 1999

by Dr. Daniel Tumas, one of the inventors of the present application.

Thus, the Declaration clearly shows that the invention claimed in the present application was conceived and reduced to practice in the United States prior to December 23, 1999. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Thompson *et al.* suggested a utility for SEQ ID NO:14 in the treatment of inflammation and inflammatory diseases (see, for example, page 4, lines 45-50). Applicants submit that the results in the MLR assay demonstrate a comparable utility for PRO1114 in in therapeutical applications when inhibition of the immune response is desired, such as in autoimmune diseases or in graft rejection.

Applicants submit that the MLR assay is well-described in standard textbooks, including, for example, *Current Protocols in Immunology*, unit 3.12; edited by J E Coligan, A M Kruisbeek, D H Marglies, E M Shevach, W Strober, National Institutes of Health, Published by John Wiley & Sons, Inc., which is referenced in Example 130, and, the entire content of which is expressly incorporated by reference into the disclosure of the present application. In brief, in this method, an immune response results upon mixing T-cells from antigenically distinct individuals under cell culture conditions. An MLR reaction can be monitored qualitatively, for example, by following the incorporation of tritiated thymidine during DNA synthesis, or, by observing blast formation, or by other methods well known in the art. That the PRO1114 polypeptide inhibits T-cell proliferation in the MLR assay is described in Example 130.

Applicants further submit that the MLR assay has been extensively used and is the best *in vitro* model for screening immunosuppressive agents for use in the prevention of graft-versus-host disease and graft rejection. It is well known that the transplantation of tissues or organs between individuals with MHC incompatibilities quickly activates the recipient's immune system which then attempts to destroy the transplanted tissue or organ. Transplantation across minor histocompatibility loci generally induces a more indolent response. Physicians analyze the major and minor histocompatibility differences to predict the success of the graft and to adjust the aggressiveness of immunosuppressive therapy.

Inhibitors of MLR find utility in suppressing unwanted immune response, and thus suppress unwanted graft rejection. For example, the ability of tepoxalin, an immunomodulatory compound, to suppress graft-versus-host reaction, has been demonstrated using the MLR assay (Fung-Leung *et al.*, *Transplantation* 60:362-8 (1995); copy enclosed). Other immunosupressants have also been routinely identified using the MLR assay. For example, the immunosuppressive efficacy of SNF4435 and D, produced by a strain of *Streptomyces spectabilis*, has been tested using the MLR assay. As recently as 2002, the immunosuppressive effect of tautomycetin (TMC) was assessed with mixed lymphocyte reactions, and confirmed *in vivo* using TMC-treated rats that received a heterotopic cardiac allograft (Shim *et al., Proc. Natl. Acad. Sci USA* 99(16):10617-10622 (2002); copy enclosed). The authors were able to conclude with confidence from the MLR data that "TMC has the capacity to inhibit the intracellular signaling pathway leading to T-cell activation and proliferation." (See page 10621, second column).

Thus, the art as a whole clearly establishes that the mixed lymphocyte reaction (MLR) is a widely used *in vitro* assay for identifying immunomodulator compounds.

Applicants further submit a declaration and supportive references from the art to support the immunoinhibitory activity of PRO1114.

Applicants submit a declaration by Sherman Fong, Ph.D. of Genentech, Inc., an expert in the field of Immunology, to show that there are specific immune inhibitor utilities for compounds identified by an MLR assay. The Declaration explains how the MLR reaction was performed in the instant application using peripheral blood mononuclear cells (PBMCs), which contain responder T-cells, and allogenic, pre-treated (irradiated) PBMCs, which predominantly contained dendritic cells. As Dr. Fong clearly states:

> It is my considered scientific opinion that a PRO polypeptide shown to inhibit T-cell proliferation in the MLR assay where the activity is observed as 80% or less of the control, as specified in the present application, would be expected to find practical utility when an inhibition of the immune response is desired, such as in autoimmune diseases.

Accordingly, the positive results obtained in this assay clearly establish the immunoinhibitory utility for the polypeptides encoded by the nucleic acids claimed in the present application, and the specification, in turn, enables one skilled in the art to use the compounds for the asserted purpose.

By the foregoing arguments and supportive evidence, Applicants have established that the MLR reaction is a generally recognized assay to assess immunoinhibitory activity. Since the legal standard accepts *in vitro* as acceptable utility and the data is "reasonably correlated" to the pharmacological utility based on the discussions above, a valid case for utility has been made and would be considered credible by a person of ordinary skill in the art.

Consequently, Applicants respectfully submit that Thompson *et al.* is not prior art under 102(e) since its effective priority date is after the invention by the Applicants for patent. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the rejection of Claims 63-65 and 68-70 under 35 U.S.C. §102(e) over Thompson *et al.* .

V. Claim Rejections Under 35 USC § 102(e) over Ni *et al.*

Claims 58-65, 69-70, and 74-77 are newly rejected as allegedly anticipated under 35 U.S.C. §102(e) by Ni *et al*, pre-grant publication U.S. 2003/0175778, with an effective priority date of June 5, 1998. The Examiner asserts that "[t]he amino acid sequence of SEQ ID NO:2 of Ni *et al.* is identical to that of the claimed polypeptide amino acid sequence of SEQ ID NO:352." The Examiner further asserts that "Ni *et al.* identifies SEQ ID NO:2 as the amino acid sequence for interferon receptor HKAEF92 and indicates that the predicted leader sequence is amino acids 1-29." The Examiner asserts that "Ni *et al.* teach a nucleic acid molecule which has 99.7% identity with the sequence of SEQ ID NO:351, therefore, the structural limitations of the claims are met." (Page 5 of the instant Office Action). The Examiner further asserts that "[s]ince the amino acid sequence of the encoded protein is identical to that of the instant specification, the functional limitations of the claims should also be met (inherent property of the protein having the amino acid sequence disclosed in the instant specification)." (Page 6 of the instant Office Action).

Applicants have claimed priority to U.S. Provisional Application Serial No. 60/087,106, filed on May 28, 1998. The present application is entitled to the priority date of May 28, 1998, which precedes by eight days the effective priority date of Ni *et al.* (June 5, 1998). Accordingly, Ni *et al.* is not prior art against the present application and Claims 58-65, 69-70, and 74-77 are patentable.

In support, Applicants respectfully submit a Declaration under 37 C.F.R. §1.131 by Dr. Baker, Dr. Goddard, Dr. Godowski, Dr. Gurney, Dr. Tumas and Dr. Wood that establishes that Applicants had cloned and sequenced PRO1114 and identified its homology to cytokine receptor family proteins before the prior art date of June 5, 1998. The consideration of the Declaration is respectfully requested.

Applicants respectfully submit that an executed copy of the Declaration will be submitted to the Examiner shortly.

U.S. Provisional Application Serial No. 60/087,106 simply needs to disclose what is disclosed in the cited reference to support the priority claim

Applicants respectfully submit that in order to overcome the 35 U.S.C. §102(a) rejection over Lal *et al.,* the Declaration by Dr. Baker, Dr. Goddard, Dr. Godowski, Dr. Gurney, Dr. Tumas and Dr. Wood ("Declaration") simply needs to provide a disclosure commensurate in scope with the disclosure in the prior art document by Ni *et al.* to support the priority claim.

In order to remove a reference as a prior art, "[i]t is sufficient if [the affidavit under Patent Office Rule 131] shows that as much of the claimed invention as is taught in the reference has been reduced to practice by the [patentee] prior to the date of the reference." *In re* Stempel, 241 F.2d 755, 757 (1957). In *In re* Stempel, the patent applicant (Stempel) had claims directed to both (i) a particular genus of chemical compounds (the "generic" claim) and (ii) a single species of chemical compound that was encompassed within that genus (the "species" claim). In support of a rejection under 35 U.S.C. §102, the examiner cited against the application a prior art reference that disclosed the exact chemical compound recited in the "species" claim. In response to the rejection, the patent applicant filed a declaration under 37 C.F.R. §1.131 demonstrating

that he had made that specific chemical compound prior to the effective date of the cited prior art reference. The Court found the applicant's 37 C.F.R. §1.131 declaration effective for swearing behind the cited reference for purposes of both the "species" claim and the "genus" claim. Specifically, the Court stated in support of its decision that "all the applicant can be required to show is priority with respect to so much of the claimed invention as the reference happens to show. When he has done that he has disposed of the reference." *Id.* at 759.

Furthermore, the Examiner is respectfully directed to *In re* Moore, 170 USPQ 260 (CCPA 1971), where the holding in *In re* Stempel was affirmed. In *In re* Moore, the patent applicant claimed a particular chemical compound in his patent application and the examiner cited against the applicant a prior art reference under 35 U.S.C. §102 rejection which disclosed the compound but did not disclose any specific utility for the compound. The patent applicant filed a declaration under 37 C.F.R. §1.131 demonstrating that he had made the claimed compound before the effective date of the cited prior art reference, even though he had not yet established a utility for that compound. On appeal, the Court indicated that the 131 declaration filed by the patent applicant was sufficient to remove the cited reference. The Court relied on the established "Stempel Doctrine" to support its decision, stating:

> An applicant need **not** be required to show [in a declaration under 37 C.F.R. §1.131] any more acts with regard to the subject matter claimed that can be carried out by one of ordinary skill in the pertinent art following the description contained in the reference ... the determination of a practical utility when one is not obvious need **not** have been accomplished prior to the date of a reference unless the reference also teaches how to use the compound it describes.

In re Moore, 170 USPQ at 267 (emphasis added).

Thus, *In re* Moore confirmed the holding in *In re* Stempel which states that in order to effectively remove a cited reference with a declaration under 37 C.F.R. §1.131, **an applicant need only show that portion of his or her claimed invention that appears in the cited reference**.

Ni *et al.* discloses a polypeptide identified as a member of the interferon receptor family and named Interferon Receptor HKAEF-92 (SEQ ID NO:2), which has 100% sequence identity

to SEQ ID NO:352 of the instant application. Ni *et al.* disclose that HKAEF-92 shares sequence similarity with several interferon (INF) receptors as shown in Figure 2. Although Ni *et al.* includes general statements regarding possible uses of the sequence, no specific examples or experimental data are provided regarding the use of SEQ ID NO:2. Therefore, since Ni *et al.* only discloses a polynucleotide sequence, the encoded polypeptide sequence, and a sequence homology, Applicants respectfully submit that the Declaration simply needs to show possession of the polypeptide sequence, its encoding polynucleotide sequence as disclosed in Ni *et al.*, and a sequence homology in order to overcome the 35 U.S.C. §102 rejection.

Applicants respectfully submit that U.S. Provisional Application Serial No. 60/087,106, filed on May 28, 1998, provides the nucleic acid and amino acid sequences of the PRO1114 polypeptide. and indicates that this amino acid sequence shares homology to cytokine receptor family proteins (see U.S. Patent Application No. 60/087,106 on page 8, under the section titled "Full-length PRO1114 polypeptides").

The Declaration clearly states that U.S. Provisional Application Serial No. 60/087,106, filed on May 28, 1998, discloses sequences designated as SEQ ID NO:1 and SEQ ID NO:3, which are identical to SEQ ID NO:351 and SEQ ID NO:352, respectively, of the above-identified application. U.S. Provisional Application Serial No. 60/087,106 also discloses that SEQ ID NO:3 has homology to cytokine receptor family proteins.

Accordingly, Applicants respectfully submit that the disclosures are commensurate in scope and that U.S. Provisional Application Serial No. 60/087,106 discloses all that the cited prior art discloses.

Consequently, based on the holdings of *In re* Stempel and *In re* Moore, Applicants respectfully submit that Ni *et al.* is not prior art under 102(e) since its effective priority date is after the invention by the Applicants for patent. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the rejection of Claims 58-65, 69-70, and 74-77 under 35 U.S.C. §102(e) over Ni *et al.*.

CONCLUSION

In conclusion, the present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Should there be any further issues outstanding, the Examiner is invited to contact the undersigned attorney at the telephone number shown below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2630 P1C90**).

Respectfully submitted,

Date: June 22, 2005

By: _____
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